Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Original Article

Chin Med Sci J
2022; 37(1): 23-30
doi:10.24920/003982

Magnetic Resonance Imaging Findings of Olfactory Bulb in Anosmic Patients with COVID-19: A Systematic Review

Atefeh Beigi-khoozani[1], Amirmohammad Merajikhah[2*], Mahdieh Soleimani[3]

[1]Department of Operating Room, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Operating Room, Sabzevar University of Medical Sciences, Razavi Khorasan, Iran
[3]Department of Operating Room, Maragheh University of Medical Sciences, East Azerbaijan, Iran

ABSTRACT

Background Anosmia is one of the symptoms in individuals with SARS-CoV-2 infection. In anosmic patients, SARS-CoV-2 temporarily alters the signaling process in olfactory nerve cells and olfactory bulb (OB), which eventually damages the structure of the olfactory epithelium, leading to a permanent disorder in the olfactory pathway that this damaged structure is showed in MRI imaging

Method Two investigators independently searched four databases consisting of PubMed, ProQuest, Scopus, and Web of Science for relevant records as of November 11, 2020 with no time, space, and language restrictions. Google Scholar was also searched for the related resources within the time limit of 2020. All the found articles were reviewed based on the PRISMA flow diagram. Qualitative studies, case reports, editorials, letters, and other non-original studies were excluded from this systematic analysis.

Results Initial search yielded 434 records. After reviewing the titles and abstracts, we selected 74 articles; finally, 8 articles were depicted to be investigated and read in full text. The obtained results showed an increase in the width and volume of the olfactory cleft (OC), complete or partial destruction of OC, and complete occlusion of OC in COVID-19 patients. Deformation and degeneration as well as a subtle asymmetry were evident in the OBs. Computed tomography (CT), meganetic resonance imaging (MRI), and positron emission tomography (PET) were used to detect the outcomes of anosmia in these studies.

Conclusions The changes in OC are greater than those in OB in patients with COVID-19, mainly due to the inflammatory and immune responses in OC. However, fewer changes in OB are due to neurological or vascular disorders. Topical steroid therapy and topical saline can be helpful.

Key words: magnetic resonance imaging; olfactory bulb; COVID-19; anosmia

INTRODUCTION

SARS-CoV-2, the virus that causes the coronavirus disease 2019 (COVID-19), was first detected in Wuhan, China, and then worldwide[1]. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic[2]. The typical clinical manifestations of COVID-19 include fever, muscle or joint pain, loss of smell (anosmia) and taste[3], and respiratory symptoms[1]. An early report in the Republic of Korea showed that about two-thirds of COVID-19 patients experienced anosmia[4]; in addition, an increasing number of patients with anosmia but without other symptoms were infected with SARS-CoV-2[5]. Many studies have demonstrated an association between olfactory dysfunction (OD) and COVID-19[4]. The prevalence of olfactory disorders varied between 14.8% and 52.73% in different patient populations[6-8]. On March 22, 2020, the American Academy of Otolaryngology proposed that anosmia be added to the list of COVID-19-related symptoms[9], and WHO recently added anosmia to its list of official symptoms[10]. Anosmia may occur 2 to 14 days after

Received August 14, 2021; accepted October 15, 2021; published online March 7, 2022.
*Corresponding author E-mail: amir.meraj74@gmail.com.

being exposed to SARS-CoV-2 or its variants[11].

Generally, angiotensin-converting enzyme 2 (ACE2) is abundant in the epithelium of the oral and nasal mucosae[12, 13]. Covered by olfactory neuroepithelium, the olfactory cleft (OC) is located between the middle turbinate and the nasal septum[14]. ACE2 and transmembrane protease serine 2 (TMPRSS2) work in stem cells residing in the olfactory epithelium and in vascular cells in the nose and olfactory bulb (OB)[15]. SARS-CoV-2 can enter the host body through respiratory mucosa or other mucosal surfaces[1]. Using its spike proteins (protein S), the virus enters human cells and binds to ACE2 in the target cells[16]. Therefore, due to the high concentrations of ACE2 and TMPRSS2 in OC and the tendency of SARS-COV-2 to bind to these receptors, the virus is transmitted through the nose to the brain[17-21]. Damage to the olfactory system can be the result of a local infection in the supporting cells that causes a temporary alteration in the signaling process in olfactory neurons and OBs, or the damage can hurt the entire structure of the olfactory epithelium and cause permanent disorder in the olfactory pathway[15]. These disorders impair the ability of patients to smell food and the environment and lower the quality of life associated with social interactions, eating, and well-being[22]. The extent to which the loss of smell and taste after SARS-CoV-2 infection is due to OC edema, structural deformation of the olfactory neuroepithelium, or direct invasion of the olfactory nerve pathways remains controversial[10, 23].

Magnetic resonance imaging (MRI) of OB is useful for evaluating patients with anosmia/hyposmia[24]. In patients with severe COVID-19, MRI may reveal the damaged OB structure that leads to local inflammatory response[25]. Brain MRI performed on anosemic COVID-19 patients shows that the anosmia may be due to central olfactory system abnormalities[26]. Furthermore, in a study in which patients underwent neuroimaging, 7 out of 37 patients were found to have OB abnormalities[27]. In this systematic review, to address the question of "what are the imaging findings of OB on magnetic resonance imaging in patients with COVID-19?", we evaluated the results of OB MRI in patients with SARS-CoV-2 infection as have been reported in literature.

MATERIALS AND METHODS

Literature searching and selection

We conducted literature searching in databases of PubMed, ProQuest, Scopus, and Web of Science for research article published in the time period till November 11, 2020. Google Scholar was also explored within the year of 2020. The keywords and the search strategy we used are [(MRI) AND (olfactory bulb) AND (COVID-19)]. All articles were collected in EndNote X8 software. Titles and abstracts of all the obtained articles were screened. The references of the eligible articles were scanned as well. Studies that focus simultaneously on anosmia and olfactory loss, OB, MRI, COVID-19, and SARS-CoV-2 were included in the study. Duplicate studies and irrelevant ones were excluded. Qualitative articles, editorials, notes, reviews, case reports, and letters were excluded.

Data collection and analysis

The full texts of the eligible articles were examined. Two researchers extracted the data include magnetic resonance imaging results of OB separately.

RESULTS

In the initial search, a total of 434 articles were found from four databases and the Google Scalar search engine. After the exclusion of 93 duplicates with the help of EndNote X8 software, 341 articles remained, Among them 332 were excluded after their titles and abstracts were reviewed and 9 studies remained for full-text screening. After reading the texts of the articles thoroughly, 8 articles were chosen and 1 article was left out. The PRISMA flow chat of literature selection is presented in **Figure 1**.

In the articles included in the study, the MRI reveale increased width and volume of OC, complete bilateral or partial destruction of OC, complete obstruction of OC, as well as subtle deformation, degeneration, and asymmetry in OB. **Table 1** summarizes the MRI findings of OC and OB in COVID-19 patients with anomia. OC structure changes caused by inflammatory and immune responses occurred more frequently than the changes in OB.

Use of topical steroids and saline and olfactory exercises help to improve anosmia, as shown in **Table 2**.

DISCUSSION

SARS-CoV-2 alters the sense of smell by affecting OC. Altundag *et al.* (2020) found the width of OC increased in COVID-19 patients with anosmia compared

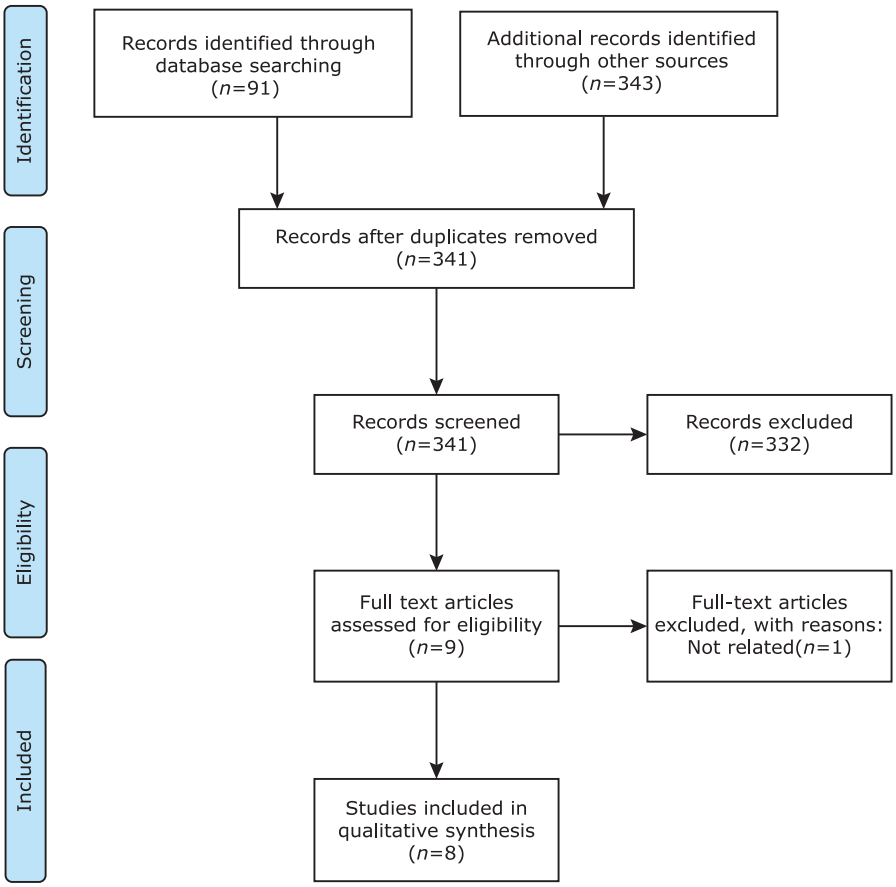

Figure 1. Flow diagram of literature screening and study selection

to the controls. In these patients, the overall volume of OC also increased, which might be associated with the increase of the ACE2 receptors on the olfactory mucosa, which causes an increase in the adhesion of the virus[28]. Due to the coronavirus uptake through ACE2 receptors, one cause of OD in these patients is an increase in OC volume. On the other hand, obstruction of olfactory mucosa in OC can cause anosmia[35]. However, in a study performed by Naeini *et al.* no significant mucosal changes and abnormalities were observed in OC on CT images[36]. Therefore, the development of a sudden anosmia and an increase in OC volume can be attributed to the rapid immune response and "nasal cytokine storm" induced by severe SARS-CoV-2 infection[37]. This reaction can also lead to localized edema of the mucosa in the OC and prevent smells from passing into the olfactory mucosa[38]. Niesen *et al.* revealed complete bilateral or partial destruction of OC in 50% of patients and unilateral or partial destruction in the rest of them; however, the presence of OC inflammation was not evident in their MRI images[30]. Nonetheless, in another study the coronavirus-induced OC inflammation was demonstrated on MRI[39]. Thus, edema or total or partial degeneration of OC can lead to olfactory dysfunction (OD). It has also been reported that inflammatory obstruction of OC may occur due to the interaction between SARS-COV-2 and the expression of the ACE2 protein in the olfactory epithelium[15]. Therefore, the loss of OC due to inflammation of the central olfactory epithelium is not the only underlying pathophysiological mechanism that can prompt SARS-CoV-2 dysosmia[40]; rather, several factors can also change the structure and function of OC and subsequently lead to OD. Eliezer *et al*. found that 95% of patients with early symptoms of COVID-19 suffered from complete obstruction of OC; they claimed that anosmia and OD happen when the aromatic molecule could not reach the olfactory epithelium, probably due to nasopharyngeal infection caused by local inflammation. However, on MRI taken after 20 days, the symptoms of complete OC obstruction were still evident; after one month of follow-up, they observed a significant reduction in OC obstruction[41,29]. Therefore, OD can happen due to swelling, eventual leading to obstruction of the

Table 1. The results of magnetic resonance imaging on the olfactory system in COVID-19 patients.

References	Study type	Number of patients	Cause of OD	Assessment		MRI manifestations	
				Odor assessment	Imaging modality	Olfactory cleft (OC)	Olfactory bulb (OB)
Klironomos S, *et al*[27]	Retrospective cohort study	185	SARS-CoV-2 infection	RT-PCR	CT and MRI	None	Abnormal OB signals
Altundag A, *et al*[28]	Prospective	91	SARS-CoV-2 infection; Non–SARS-CoV-2 infection	RT-PCR; Sniffin' sticks test	CT and MRI	Increased widths and volume of OC	No significant difference in OB volumes and olfactory sulcus depths on MRI among anosmic patients
Eliezer M, *et al*[29]	Prospective case-controlled	20	SARS-CoV-2 infection	PCR; Visual Olfactive Score (VOS)	MRI	Complete obstruction of the OC occured in 95% of patients at the early stage; no obstruction was seen was seen during the 1-month follow-up	On the first MRI session, no significant difference in OB volume. At the 1-month follow-up visit, no significant difference in OB volume. Normal morphology of the OB
Niesen M, *et al*[30]	Prospective	12	SARS-CoV-2 infection	RT-PCR	PET; MRI with fluorodeoxyglucose	Bilateral obliteration of the OC in 50% of patients	Subtle asymmetry in OB
Kandemirli SG, *et al*[31]	Prospective	23	COVID-19	PCR; Sniffin' sticks test	CT; MRI	High rate of OC opacification	Reduction in OB volume; altered OB shape; signal abnormalities
Aragão MFVV, *et al*[32]	Retrospective	5	SARS-CoV-2 infection	Not performed	MRI with contrast enhancement	None	Abnormal OB intensities in all patients
Brookes N, *et al*[33]	Case series	4	COVID-19	University of Pennsylvania Smell Identification Test (UPSIT)	MRI	None	In two cases, MRI showed normal OB and cribriform plates, along with minimal mucosal thickening in the ethmoid sinuses.
Coolen T, *et al*[34]	Prospective, case series	19	SARS-CoV-2 infection	PCR; chest CT	MRI and PET	Asymmetric olfactory bulb was observed, with or without obliteration of OC. Obliteration of OC and ipsilateral inflammation of OB	Asymmetric OB, inflation of OB

OD: olfactory dysfunction; RT-PCR: reverse transcription polymerase chain reaction; MRI: magnetic resonance imaging; PET: positron emission tomography; CT: computed tomography

Table 2 Treatments and outcomes of patients treated with topical steroids or saline

Medicines in treatment	Route of administration	Recovery time		Duration of effectiveness	Result of G immunoglobulin
		Partial	Total		
Steroids	Oral	1 week (40% - 85%)	2 - 3 weeks	7 days	Positive
Steroid drops	Local	1 week (40% - 85%)	2 - 3 weeks	7 days	Positive
Ephedrine	Local	1 week (85%)	2 weeks	3 days	Positive
Betnesol	Local	1 week (85%)	2 weeks	3 days	Positive
Prednisolone	Oral	6 days	2 weeks	3 days	Positive
Nasal saline irrigations	Local	8 days	2 weeks	8 days	None

olfactory pathway, which may or may not be seen on MRI.

Structural changes of OB in patients with COVID-19 are evident on MRI. Kandemirli *et al*. (2020) showed deformation and degeneration of OB and emphasized that the high rate of OB degeneration was due to direct/indirect damage to the pathway of olfactory neurons. It is also particularly one of the reasons that can be attributed to patients with prolonged anosmia[31]. In general, the causes of anosmia can be classified into two groups: a) loss of conductive or sensorineural olfactory, which is a conduction disorder associated with the destruction of the airway in the nose; and b) damage of the sensorineural pathway, which is related to olfactory epithelium with longer lasting effects until it heals[42].

In another study, OB enlargement was shown in the second stage of MRI, although there was no change in OB during the one-month follow-up. Eventually, the OB change was considered to be due to the invasion of SARS-COV-2 into the brain by the cribriform plate, which is close to OB and the olfactory epithelium[29]. Based on the available evidence, the virus mainly affects the cerebral cortex and hypothalamus[43].

On the other hand, there were studies that did not show significant changes in OB. Niesen *et al*. (2020) found only three out of 12 COVID-19 patients showed subtle asymmetry in OB, so they considered that the development of severe anosmia in these patients was not due to the changes in OB and OB disorder was not involved in olfactory loss[30]. OB changes on MRI can be attributed to infection of vascular pericytes in OB, as ACE2 is expressed there[15]. On the other hand, Cao *et al*. (2019) showed that the receptor of ACE2 gene polymorphism in Asian and European populations can cause disease in patients with different periods[44]. In addition, in this regard, a study showed that there was no significant difference in OB volume in patients with COVID-19[28]. However, studies conducted so far have shown that OB volume decreased due to damage to olfactory receptor in post-viral anosmia[45,46]. Laurendon *et al*. revealed the increase in OB volume was associated with COVID-19. It was also shown that the volume and the intensity of the MRI signal returned to normal on the 24th day of the disease. Notably, there was no significant change in OB and signal in COVID-19-related anosmia[47]. According to the existing hypotheses, disruption in signaling to OB in the early days can be attributed to infection of sustentacular cells, which leads to disruption in signaling from olfactory sensory neurons to OB, and the sustentacular cells support the olfactory sensory neurons by maintaining ion balance. Thus, when these cells are destroyed by infection, CILIA of the olfactory sensory neurons is destroyed and signal transmission is disrupted[48].

The most common treatments for OD include: a) Olfactory training: it includes frequent and intentional inhalation of a set of smells (usually lemon, rose, clove, and eucalyptus) for 20 seconds each time, at least twice a day for at least 3 months (or more if possible)[49]. b) Nasal lavage with saline[50]: medications that have shown to be effective in treating post-infectious OD also consist of intranasal vitamin A, which may enhance olfactory neurogenesis, intranasal sodium citrate, which seems to moderate olfactory receptor transduction cascades, and systemic Omega-3, which may function as anti-inflammatory or neurodegenerative[49]. c) Nasal or oral corticosteroids[50]: a recent study showed that oral prednisolone consumption after the course of the disease, when the PCR test is negative, can be effective in improving anosmia[51].

Oral steroids are commonly used to treat anosmia. However, these drugs may impair the immune system and thus their use needs to be individualized[52]. As the exact cause of anosmia in

COVID-19 patients is still unknown, there is no concesus on its definitive treatment[51]. In some studies, corticosteroids are not recommended for people with post-infection OD. However, for patients who have been taking intravenous or intranasal steroids before COVID-19, such therapies should be continued[49]. Plasma therapy is not effective in treating anosmia[48].

A major limitation of our current study was that documented evidence in case reports was ruled out in this systematic review.

To sum up, as shown by MRI of the olfactory system in patients with COVID-19, the changes that happened in the OC due to COVID-19 are greater than those in the OB and can be attributed to inflammatory responses, immune responses, or the abundance of the olfactory epithelium in the OC structure, whereas small changes or no change in OB due to anosmia in these patients can be attributed to neurological or vascular disorders.

Conflict of interests

The authors disclosed no conflicting interest.

Author contributions

AB is the author of the letter structure and the second resource researcher; AM is the scientific author and owner of the idea letter; MS is the resource researcher.

REFERENCES

1. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. Chin Med Associat 2020; 83 (3):217-20. doi: 10.1097/jcma.0000000000000270.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 11 March 2020. Available from https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed March 5, 2021.
3. Struyf T, Deeks JJ, Dinnes J, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database Syst Rev 2020; 7(7):CD013665. doi: 10.1002/14651858.CD013665.
4. Rocke J, Hopkins C, Philpott C, et al. Is loss of sense of smell a diagnostic marker in COVID-19: A systematic review and meta-analysis. Clini Otolaryngol 2020; 45 (6):914-22. doi: https://doi.org/10.1111/coa.13620.
5. Hopkins C, Kumar N. Loss of sense of smell as marker of COVID-19 infection. The Royal College of Surgeons of England: British Rhinological Society 2020. http://www.entuk.com/_userfiles/pages/files/loss_of_sense_of_Smell-_as_marker_of_covid.pdf
6. Tong JY, Wong A, Zhu D, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and Meta-analysis. Otolaryngology–Head and Neck Surgery 2020; 163 (1): 3-11. doi: 10.1177/0194599820926473.
7. Al-Ani RM, Acharya D. Prevalence of anosmia and ageusia in patients with COVID-19 at a primary health center, Doha, Qatar. Ind J Otolaryngol Head Neck Surg 2020; 1-7. doi: 10.1007/s12070-020-02064-9.
8. Mishra P, Gowda V, Dixit S, et al. Prevalence of New Onset Anosmia in COVID-19 Patients: Is The Trend Different Between European and Indian Population? Ind J Otolaryngol Head Neck Surg 2020; 72 (4):484-87. doi: 10.1007/s12070-020-01986-8.
9. American Academy of Otolaryngology-Head and Neck Surgery. Anosmia, hyposmia, and dysgeusia symptoms of coronavirus disease. Available from https://www.entnet.org/content/aao-hns-anosmia-hyposmia-and-dysgeusia-symptomscoronavirus-disease. Accessed May 1, 2020.
10. Lechner M, Chandrasekharan D, Jumani K, et al. Anosmia as a presenting symptom of SARS-CoV-2 infection in healthcare workers–a systematic review of the literature, case series, and recommendations for clinical assessment and management. Rhinology 2020; 58(4):394-9. doi: 10.4193/Rhinzo.189.
11. US CfDCa. Symptoms of COVID-19. Available from https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed April 17, 2020.
12. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12(1): 8. doi: 10.1038/s41368-020-0074-x.
13. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020; 26 (5):681-7. doi: 10.1038/s41591-020-0868-6.
14. Geurkink N. Nasal anatomy, physiology, and function. J Allergy Clin Immunol 1983; 72(2):123-128.
15. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020; 6(31):eabc5. doi: 10.1101/2020.03.25.009084.
16. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England) 2020; 395 (10224): 565-74. doi: 10.1016/s0140-6736(20)30251-8.
17. Jahanshahlu L, Rezaei N. Central nervous system involvement in COVID-19. Arch Med Res. 2020; 51:721-2. doi: 10.1016/j.arcmed.2020.05.016.
18. Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol 2020; 84(106560):1-6. doi: 10.1016/j.intimp.2020.106560.
19. Yazdanpanah N, Saghazadeh A, Rezaei N. Anosmia: a missing link in the neuroimmunology of coronavirus disease 2019

(COVID-19). Rev Neurosci 2020; 1.
20. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020; 323(23):2427-9. doi: 10.1001/jama.2020.8707.
21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181(2):271-80. e8. doi: 10.1016/j.cell.2020.02.052.
22. Boesveldt S, Postma EM, Boak D, et al. Anosmia: A clinical review. Chem Senses 2017; 42 (7):513-23. doi: 10.1093/chemse/bjx025.
23. Moran DT, Jafek BW, Eller PM, et al. Ultrastructural histopathology of human olfactory dysfunction. Microscopy Res Tech 1992; 23 (2): 103-110.
24. Galougahi MK, Ghorbani J, Bakhshayeshkaram M, et al. Olfactory bulb magnetic resonance imaging in SARS-CoV-2-induced anosmia: the first report. Acad Radiol 2020; 27(6): 892-3. doi: 10.1016/j.acra.2020.04.002.
25. Chetrit A, Lechien JR, Ammar A, et al. Magnetic resonance imaging of COVID-19 anosmic patients reveals abnormalities of the olfactory bulb: Preliminary prospective study. J infect 2020; 81(5):816-46. doi: 10.1016/j.jinf.2020.07.028.
26. Girardeau Y, Gallois Y, De Bonnecaze G, et al. Confirmed central olfactory system lesions on brain MRI in COVID-19 patients with anosmia: a case-series. medRxiv 2020; 2020.2007.2008.20148692. doi: 10.1101/2020.07.08.20148692.
27. Klironomos S, Tzortzakakis A, Kits A, et al. Nervous System Involvement in COVID-19: Results from a Retrospective Consecutive Neuroimaging Cohort. Radiology 2020; 202791. doi: 10.1148/radiol.2020202791.
28. Altundag A, Yıldırım D, Sanli DET, et al. Olfactory cleft measurements and COVID-19-related anosmia. Otolaryngol Head Neck Surg 2021; 164(6): 1337-44. doi: 10.1177/0194599820965920. Epub 2020 Oct 13.
29. Eliezer M, Hamel AL, Houdart E, et al. Loss of smell in COVID-19 patients: MRI data reveals a transient edema of the olfactory clefts. Neurology 2020; 95(23): e3145-e3152. doi: 10.1212/WNL.0000000000010806.
30. Niesen M, Trotta N, Noel A, et al. Structural and metabolic brain abnormalities in COVID-19 patients with sudden loss of smell. Eur J Nucl Med Mol Imaging 2021; 48(6):1890-901. doi: 10.1007/s00259-020-05154-6.
31. Kandemirli SG, Altundag A, Yildirim D, et al. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. Acad Radiol 2021; 28(1):28-35. doi: 10.1016/j.acra.2020.10.006.
32. Aragão MFVV, Leal MC, Cartaxo Filho OQ, et al. Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. Am J Neuroradiol 2020; 41 (9):1703-6. doi: 10.3174/ajnr.A6675.
33. Brookes NRG, Fairley JW, Brookes GB. Acute olfactory dysfunction—A primary presentation of COVID-19 infection. Ear Nose Throat J 2020; 99 (9):94-8. doi: 10.1177/0145561320940119.
34. Coolen T, Lolli V, Sadeghi N, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. Neurology 2020; 95 (14): e2016-e2027. doi: 10.1212/WNL.0000000000010116.
35. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology 2020; 58 (3): 299-301. doi: 10.4193/rhin20.114.
36. Naeini AS, Karimi-Galougahi M, Raad N, et al. Paranasal sinuses computed tomography findings in anosmia of COVID-19. Am J Otolaryngol 2020; 41(6):102636. doi: 10.1016/j.amjoto.2020.102636.
37. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. ACS Chemical Neuroscience 2020; 11 (9): 1200-1203. doi: 10.1021/acschemneuro.0c00172.
38. Jalessi M, Barati M, Rohani M, et al. Frequency and outcome of olfactory impairment and sinonasal involvement in hospitalized patients with COVID-19. Neurol Sci 2020; 41(9):2331-8. doi: 10.1007/s10072-020-04590-4.
39. Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19. JAMA Otolaryngol Head Neck Surg 2020; 146(7):674-5. doi: 10.1001/jamaoto.2020.0832.
40. Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the chemical senses: supporting players take center stage. Neuron 2020; 107(2): 219-33. doi: 10.1016/j.neuron.2020.06.032.
41. Trotier D, Bensimon JL, Herman P, et al. Inflammatory Obstruction of the Olfactory Clefts and Olfactory Loss in Humans: A New Syndrome? Chemi Senses 2007; 32(3):285-92. doi: 10.1093/chemse/bjl057.
42. Han AY, Mukdad L, Long JL, et al. Anosmia in COVID-19: mechanisms and significance. Chem senses 2020; 45(6): 423-8. doi: 10.1093/chemse/bjaa040.
43. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Experi Med 2005; 202(3):415-24. doi: 10.1084/jem.20050828.
44. Cao Y, Li L, Feng Z, Wan S, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell discovery 2020; 6(1): 1-4. doi: 10.1038/s41421-020-0147-1.
45. Rombaux P, Mouraux A, Bertrand B, et al. Olfactory function and olfactory bulb volume in patients with postinfectious olfactory loss. The Laryngoscope 2006; 116(3):436-9. doi: 10.1097/01.MLG.0000195291.36641.1E.
46. Mueller A, Rodewald A, Reden J, et al. Reduced olfactory bulb volume in post-traumatic and post-infectious olfactory dysfunction. Neuroreport 2005; 16(5):475-8. doi: 10.1097/00001756-200504040-00011.
47. Laurendon T, Radulesco T, Mugnier J, et al. Bilateral transient olfactory bulb edema during COVID-19–related anosmia. Neurology 2020; 95(5):224-5. doi: 10.1212/WNL.0000000000009850.
48. Zheng J, Wong LYR, Li K, et al. COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. Nature 2021; 589(7843):603-7. doi: 10.1038/s41586-020-2943-z.

49. Whitcroft KL, Hummel T. Olfactory Dysfunction in COVID-19: Diagnosis and Management. JAMA 2020; 323 (24): 2512-4. doi: 10.1001/jama.2020.8391.
50. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Archives Oto-Rhino-Laryngol 2020; 277(8):2251-61. doi: 10.1007/s00405-020-05965-1.
51. Touisserkani SK, Ayatollahi A. Oral corticosteroid relieves post-COVID-19 anosmia in a 35-year-old patient. Case Rep Otolaryngol 2020; 2020: 5892047. doi: 10.1155/2020/5892047.
52. Tanasa IA, Manciuc C, Carauleanu A, et al. Anosmia and ageusia associated with coronavirus infection (COVID-19)-what is known? Experi Thera Med 2020; 20(3):2344-7. doi: 10.3892/etm.2020.8808.

(Edited by Liangjun Gu)

Open Access

To support authors with their research being widely disseminated and making maximum influence, *Chin Med Sci J* is transitioning to an open access (OA) publication. Start from March 2022, all submitted manuscripts, if accepted, will be published on *Chin Med Sci J* under a Creative Commons Attribution license (CC BY-NC), which means the content of OA article can be publicly read, downloaded, copied, distributed, translated, and adapted immediately after publication without permission from the journal. Authors retain the copyright of their article, grant an exclusive license to the editorial office of *Chin Med Sci J* as the original publisher, and grant any third part the right to use the article freely for non-commercial purpose, provided the authors of the article and the journal are given credits. Appropriate citation to the article is required and a link to the article on the journal's website is suggested.

Corresponding author shall sign the Publication License Agreement on behalf of all authors. Once a manuscript has been accepted, the article processing charge (APC) is payable at a rate of 800 CNY (for Chinese authors) or 150 USD (for overseas authors) per typeset page. APC waivers and discounts are available for authors in particular case.

Editorial Office
Chinese Medical Sciences Journal
9 Dongdan Santiao, Beijing 100730, China
Tel: 86-10-65105897
Fax: 86-10-65133074
E-mail: cmsj@pumc.edu.cn
March 10, 2022